(4+3)-Cycloaddition of Donor-Acceptor Cyclopropanes with Thiochalcones: A Diastereoselective Access to Tetrahydrothiepines

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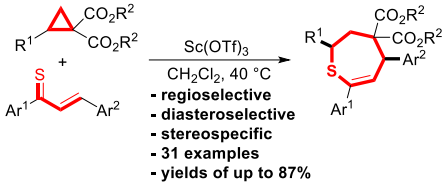
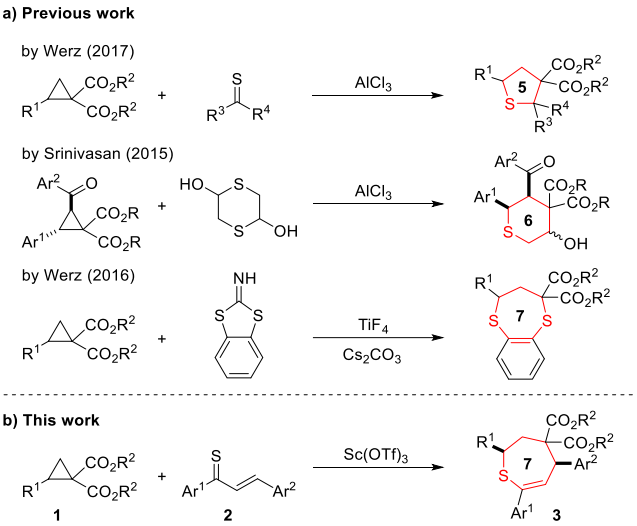
Supporting Information Placeholder



ABSTRACT: A general approach is described for the formation of tetrahydrothiepines using donor-acceptor cyclopropanes. Thiochalcones, functioning as sulfur-containing four-atom building blocks, were reacted in a Lewis-acid-catalyzed formal (4+3)-cycloaddition reaction with donor-acceptor cyclopropanes as three-atom building blocks. Under mild conditions various tetrahydrothiepines were synthesized in good yields in a stereosepecific reaction with high functional group tolerance.

Donor-acceptor (D-A) cyclopropanes are easily available building blocks and have been widely used as masked 1,3-zwitterions in organic synthesis and methodology. The first observations about the special reactivity of these highly strained molecules[1] were made in the late 1970s by Wenkert and Reissig.[2] However, only recently have many groups employed these three-membered entities, bearing a donor and acceptor moiety in adjacent positions, for various transformations.[3] The C-C single bond between the donor- and the acceptor-substituted carbon atoms is easily cleaved, paving the way for an increasing number of reactions ranging from rearrangements[4] and ring-opening reactions[5] to cycloadditions; the latter type in particularly has been widely explored in the recent past. Besides (3+2)-cycloadditions incorporating e.g. alkenes,[6] alkynes,[7] carbonyls,[8] heterocumulenes[9] and others,[10] (3+3)-[11] and (4+3)-cycloadditions[12] have become of interest, but are still rare. In this regard, D-A cyclopropanes have been successfully utilized for the synthesis of oxygen- and nitrogen-containing heterocycles by cycloaddition reactions; however, the construction of sulfur-containing heterocycles by the use of D-A cyclopropanes has still not been extensively investigated. Our group has demonstrated a simple and efficient strategy to form thiolanes by a hetero-(3+2)-cycloaddition of D-A cyclopropanes **1** with thioketones,[13] while other groups later contributed the insertion of thionoesters[14] and thiourea (Scheme 1).[15] Srinivasan obtained the six-membered analogs by using in situ generated mercaptoaldehyde.[16] Employing benzodithioloimines as surrogates for *ortho*-bisthioquinones furnished benzannulated seven-membered heterocycles with two embedded sulfur atoms.[17]

Scheme 1. Previous Work on the Formation of Sulfur-Containing Heterocycles via D-A Cyclopropane Chemistry and Our Novel Approach to Tetrahydrothiepines



To complement the ranks of these transformations, we were interested in designing a method for the formation of tetrahydrothiepines **3** by employing thiochalcones **2** as sulfur-containing four-atom building blocks. We envisioned that under suitable conditions D-A cyclopropanes would undergo a formal (4+3)-cycloaddition reaction to give the unsaturated seven-

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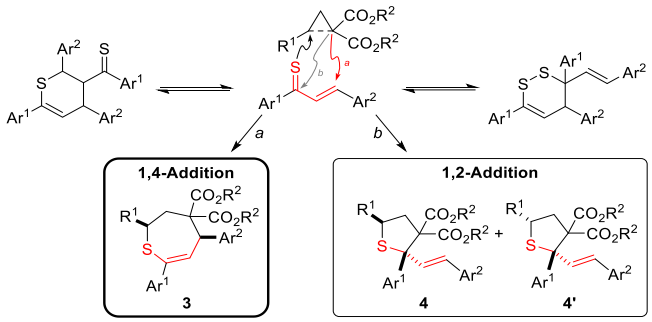
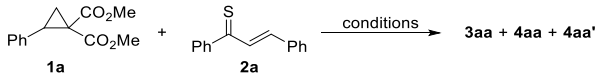
membered ring system (Scheme 1). Thiochalcones are known to exist in an equilibrium with two different dimers which are obtained by a reversible thia-Diels-Alder reaction (Scheme 2); they have already been utilized as two- or four-atom building blocks in numerous cycloaddition reactions, e.g. with nitrile imines,[18] alkynes,[19] dienamines,[20] or α-nitroalkenes.[21] Under fine-tuned conditions we expected that the monomeric form of thiochalcone would be able to undergo an (n+3)-cycloaddition process, whereby the formation of the five-membered 1,2-addition products **4** and **4'** is suppressed by a carefully chosen Lewis acid to provide only the desired seven-membered sulfur heterocycles **3**.

Scheme 2. Possible Reaction Pathways



We started our investigations by using cyclopropane **1a** and the parent thiochalcone **2a** as model substrates for our anticipated (4+3)-cycloaddition reaction. At room temperature in dichloromethane a selection of commonly used Lewis acids showed no conversion of cyclopropane **1a** (see Supporting Information). The first successful results were achieved with aluminum salts such as $AlCl_3$ and $Al(OTf)_3$. However, the undesired five-membered ring products were still formed in significant amounts (Table 1, entries 1-2).

Table 1. Optimization of the Reaction Conditions[a]



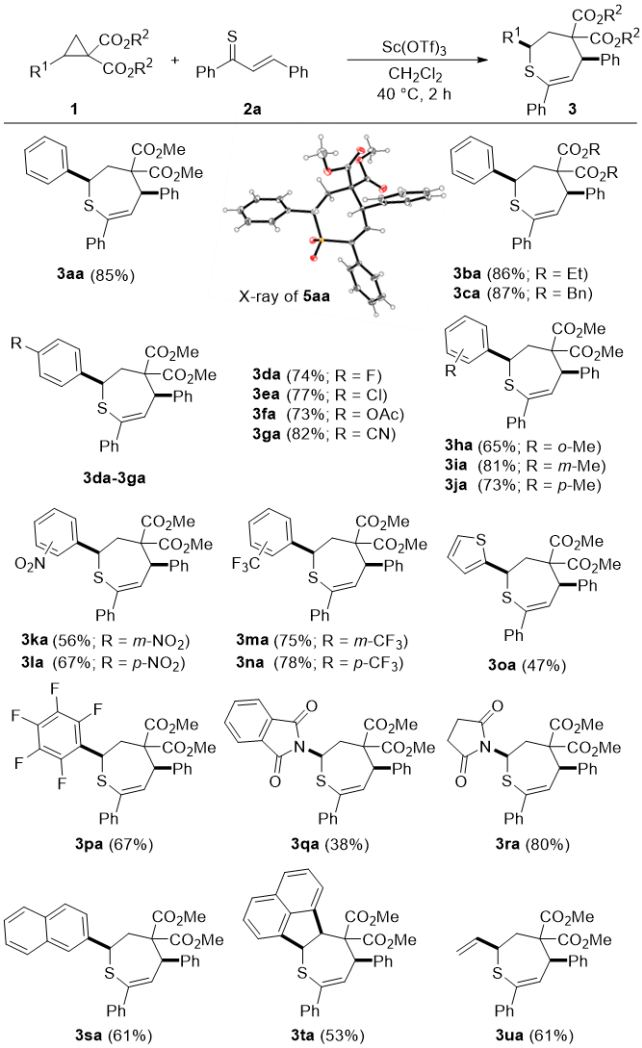
Entry	Lewis acid	Solvent	T (°C)	Yield (%)[b] 3aa	4aa	4aa'
1	$AlCl_3$	CH_2Cl_2	rt	41	7	8
2	$Al(OTf)_3$	CH_2Cl_2	rt	10	14	23
3	$TiCl_4$	CH_2Cl_2	rt	--	--	24
4	$Sc(OTf)_3$	CH_2Cl_2	rt	(76)	--	--
5	$Sc(OTf)_3$	DCE	rt	(69)	--	--
6	$Sc(OTf)_3$	Dioxane	rt	--	25	52
7	$Sc(OTf)_3$	Toluene	rt	12	23	36
8	$Sc(OTf)_3$	Et_2O	rt	--	14	63
9	$Sc(OTf)_3$	CH_2Cl_2	10	40	28	19
10	**$Sc(OTf)_3$**	**CH_2Cl_2**	**40**	**(85)**	--	--
11[c]	$Sc(OTf)_3$	CH_2Cl_2	40	(75)	--	--

[a]Reaction conditions: **1a** (100 µmol), **2a** (180 µmol), Lewis acid (20 mol%), solvent (1.5 mL), under Ar, 12 h; DCE = 1,2-dichloroethane. [b]Yields (± 3%) refer to ^{1}H NMR yields; yields in brackets refer to purified and isolated products. [c]**2a** (230 µmol) was used.

Notably, titanium tetrachloride $TiCl_4$ delivered exclusively the tetrahydrothiophene **4aa'** (entry 3), whereas $Sc(OTf)_3$ finally gave our desired product **3aa** in a surprisingly good yield of 76% (entry 4). Next, we tested the influence of the solvent system. Dichloroethane gave similar results, whereas dioxane, toluene and diethyl ether afforded various mixtures (entries 5-8). The optimal temperature was found to be 40 °C, in the presence of 1.8 equivalents of crude thiochalcone **2a** (entries 9-10). Remarkably, under these conditions tetrahydrothiepine **3aa** was isolated in 85% yield. In all cases only one diastereomer of the seven-membered ring was observed (*cis*-arrangement of R^1 and Ar^2).

Having found suitable reaction conditions, the generality of our transformation was explored (Scheme 3). First, a large variety of D-A cyclopropanes were evaluated. We started with a modification of the ester acceptor (R^2) at the cyclopropane **1**. Thus, our model system was decorated with ethyl and benzyl esters (**3ba-ca**); both derivatives delivered the desired tetrahydrothiepines in very good yields.

Scheme 3. (4+3)-Cycloaddition Reaction with Respect to Various D-A Cyclopropanes[a]



[a]Reaction conditions: **1** (100 µmol), **2a** (180 µmol), $Sc(OTf)_3$ (20 mol%), CH_2Cl_2 (1.5 mL), under Ar, 2 h; yields refer to purified and isolated products.

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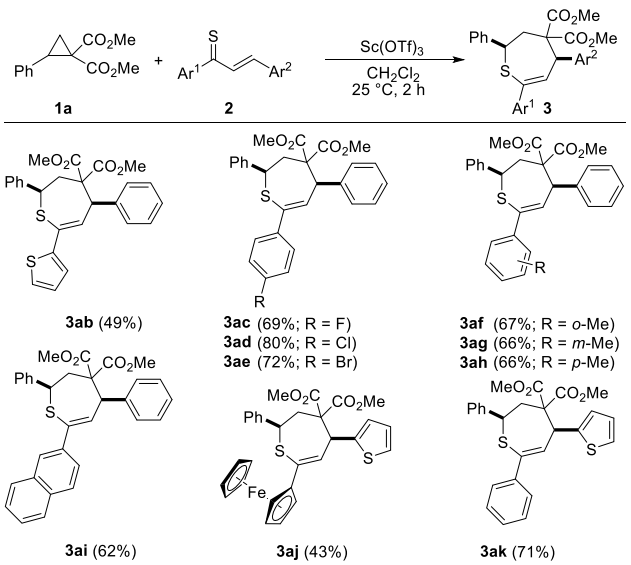
Next, we tested different *para*-substituents of the phenyl moiety. The transformation proceeded smoothly with fluoro, chloro, acetoxy and nitrile groups (**3da-ga**) in comparable yields of 73-82%. Methyl substitution in *ortho*-, *meta*- and *para*-position furnished the seven-membered rings in 65-81% yield (**3ha-ja**). Next, we decorated the system with electron-withdrawing nitro and trifluoromethyl groups in *meta*- and *para*-position. Whereas the CF_3 group gave **3ma** and **3na** in good yields, the nitro-substituted compounds (**3ka-3la**) were obtained in only moderate yields. Heteroaryls such as the thienyl residue also allowed the transformation; however, the yield of **3oa** dropped to 47%, whereas the highly electron-deficient perfluorophenyl donor performed remarkably well, furnishing **3pa** in 67% yield.

The phthalimide donor (**3qa**) showed only low conversion; in contrast, related succinimide donors (**3ra**) act as suitable residues to promote the (4+3)-cycloaddition reaction in 80% yield. Increasing or decreasing the π-system provided the desired products **3sa-3ua** in moderate yields. Finally, the crystal structure of **5aa**, the sulfone derived from **3aa**, unambiguously proved the formation of the seven-membered ring system and confirms the arrangement of both phenyl groups pointing in the same direction.

Spurred on by these results, we were keen to test various thiochalones bearing aryl- and heteroaryl moieties (Scheme 4). Decoration of the thiochalone with a thienyl residue next to the thiocarbonyl afforded **3ab** in moderate yield, whereas the same residue in the 4-position delivered **3ak** in a much better yield of 71%. A combination of ferrocenyl and thienyl group (**3aj**) provided the product in 43% yield. Substitution in *ortho*-, *meta*- and *para*-position (**3af-3ah**) with a methyl group had no greater influence and proceeded smoothly with 66%, 66% and 67% yield. Interestingly, substitution of the phenyl core in *para*-position gave moderate to very good yields depending on the type of substituent (**3ac-3ae**). A yield of 62% was achieved by using a naphthyl group in 2-position (**3ai**).

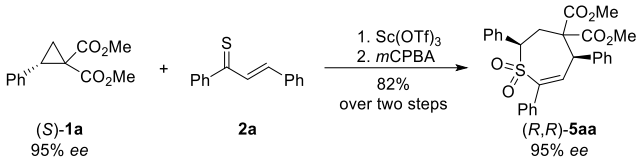
Scheme 4. (4+3)-Cycloaddition with Respect to Various Thiochalcones[a]



[a]Reaction conditions: **1a** (100 µmol), **2** (180 µmol), $Sc(OTf)_3$ (20 mol%), CH_2Cl_2 (1.5 mL), under Ar, 2 h; yields refer to purified and isolated products.

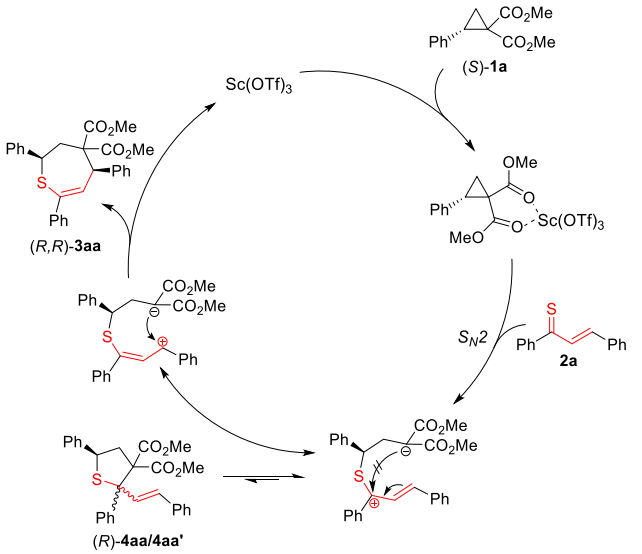
On several occasions we noticed that the ring-closing step seems to be reversible. To shed light on the reaction mechanism, we conducted further control experiments (Scheme 5). Initially, we tested the stereospecificity of our transformation by using enantioenriched cyclopropane (*S*)-**1a** (95% *ee*). To our disappointment baseline separation of (*rac*)-**3aa** by chiral HPLC was not successful. Thus, a further transformation to sulfone (*R*,*R*)-**5aa** was necessary. To our delight the stereoinformation is completely transferred during the transformation (95% *ee* of the product). To prove the reversibility of the ring-closure we subjected $Sc(OTf)_3$ to the isolated by-products (**4aa** and **4aa'**), stirring the mixtures for 2 h at 40 °C; we were indeed able to observe the transformation to the corresponding other products by NMR spectroscopy (see Supporting Information).

Scheme 5. Stereospecificity Experiment



Based on these findings, we propose the following reaction mechanism (Scheme 6). D-A cyclopropane (*S*)-**1a** is activated by $Sc(OTf)_3$ and thus paves the way for an S_N2-like attack of thiochalcone **2a**. Under inversion of configuration a zwitterion is formed with a delocalized positive charge. Kinetically favored five-membered ring-closure furnishes the undesired side products (*R*)-**4aa** and (*R*)-**4aa'**. Higher temperatures favor the attack at the terminal less-hindered carbon of the allyl system, leading to the thermodynamically favored seven-membered product (*R*,*R*)-**3aa** after releasing the Lewis acid.

Scheme 6. Proposed Mechanism



In conclusion, we have demonstrated a protocol for the construction of tetrahydrothiepines by a Lewis-acid-catalyzed (4+3)-cycloaddition reaction. Thiochalcones were employed as sulfur-containing four-atom building blocks. The transformation proceeded smoothly with high functional group toler-

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ance and under mild conditions in a stereospecific manner. Under the given reaction conditions the formation of the undesired five-membered ring analogs is minimized and the seven-membered ring system is obtained as a single diastereomer.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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